1: Am J Hum Genet 1998 Mar;62(3):641-52 Related Articles, Nucleotide, OMIM, Protein, Books, LinkOut

The University of Chicago Press

Localization of the fourth locus (GLC1E) for adult-onset primary open-angle glaucoma to the 10p15-p14 region.

Sarfarazi M, Child A, Stoilova D, Brice G, Desai T, Trifan OC, Poinoosawmy D, Crick RP.

Department of Surgery, University of Connecticut Health Center, Farmington, CT 06030-1110, USA. msarfara@cortex.uchc.edu

One of the major causes of blindness is primary open-angle glaucoma, which affects millions of elderly people worldwide. Genetic studies have so far mapped three loci for the adult-onset form of this condition to the 2cen-q13, 3q21-q24, and 8q23 regions. Herein, we report the localization of a fourth locus, to the 10p15-p14 region, in one large British family with a classical form of normal-tension open-angle glaucoma. Of the 42 meioses genotyped in this pedigree, 39 subjects (16 affected) inherited a haplotype compatible with their prior clinical designation, whereas the remaining 3 were classified as unknown. Although a maximum LOD score of 10.00 at a recombination fraction of straight theta=.00 was obtained with D10S1216, 21 other markers provided significant values, varying between 3.77 and 9.70. When only the affected meioses of this kindred were analyzed, LOD scores remained statistically significant, ranging from 3.16 (D10S527) to 3.57 (D10S506). Two critical recombinational events in the affected subjects positioned this new locus to a region of approximately 21 cM, flanked by D10S1729 and D10S1664. However, an additional recombination in a 59-year-old unaffected female suggests that this locus resides between D10S585 (or D10S1172) and D10S1664, within a genetic distance of 5-11 cM. However, the latter minimum region must be taken cautiously, because the incomplete penetrance has previously been documented for this group of eye conditions. A partial list of genes that positionally are considered as candidates includes NET1, PRKCT, ITIH2, IL2RA, IL15RA, IT1H2, hGATA3, the mRNA for open reading frame KIAA0019, and the gene for D123 protein.

PMID: 9497264 [PubMed - indexed for MEDLINE]

1: Oncogene 1998 Jan 15;16(2):257-63

Structural and functional evidence for the presence of tumor suppressor genes on the short arm of chromosome 10 in human gliomas.

Kon H, Sonoda Y, Kumabe T, Yoshimoto T, Sekiya T, Murakami Y.

Oncogene Division, National Cancer Center Research Institute, Tokyo, Japan.

Loss of heterozygosity (LOH) observed at polymorphic loci on both arms of chromosome 10 in many human gliomas suggests the presence of multiple tumor suppressor genes on this chromosome. Recently, the PTEN/MMAC1 gene on 10q23 was isolated as one of these putative glioma suppressors. To determine the subchromosomal localization of others, we analysed 79 gliomas for LOH using 30 polymorphic microsatellite markers on the short arm and 10 markers on the long arm of chromosome 10. Twenty tumors showed LOH at all the loci examined, while 17 others showed LOH at loci on a portion of chromosome 10. Deletion mapping of the latters demonstrated that two distinct regions, encompassing genetic distances of 5.6 cM on 10p15 and 5.5 cM on 10p14, were lost frequently. Introduction of chromosomal fragments 10p14-p15, which included the entire region on 10p15 and a portion of that on 10p14 assigned by deletion mapping, into the human glioblastoma cell line T98G through microcell-mediated chromosome transfer markedly suppressed colony forming ability in soft agar compared with parental T98G cells. The combined results of structural and functional analyses strongly suggest that aberrations of the tumor suppressor gene(s) within chromosomal region 10p14-p15 are involved in development of human gliomas.

PMID: 9464544 [PubMed - indexed for MEDLINE]

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1: Genes Chromosomes Cancer 1997 Oct;20(2):167-72 Related Articles, Books, LinkOut

Fine mapping of a region of common deletion on chromosome arm 10p in human glioma.

Voesten AM, Bijleveld EH, Westerveld A, Hulsebos TJ.

Institute of Human Genetics, Academic Medical Center, University of Amsterdam, The Netherlands.

Allelic loss on chromosome 10 is a frequent event in high grade gliomas. Earlier studies have shown that in most cases a complete copy of chromosome 10 is lost in the tumor. To define more accurately and specifically the region of common deletion on chromosome arm 10p, we have screened a large series of gliomas for allelic losses that exclusively affect this part of the chromosome. Allelic loss profiles were determined for 127 gliomas, including 118 astrocytomas of various malignancy grades. Seventeen tumors displayed loss of part of chromosome 10. In three of these, only chromosome arm 10p sequences were lost. The interval between loci D10S559 and D10S435 in 10p15, with a length of approximately 800 kilobase pairs, was commonly deleted in the latter tumors, suggesting that this region may harbor a tumor suppressor gene important in glioma tumorigenesis. Comparison of the allelic loss profiles in the low and high grade astrocytomas revealed that astrocytoma progression is associated with increased loss of chromosome 10 sequences.

PMID: 9331567 [PubMed - indexed for MEDLINE]

1: Genes Chromosomes Cancer 1997 Feb;18(2):115-25

Detection of DNA gains and losses in primary endometrial carcinomas by comparative genomic hybridization.

Sonoda G, du Manoir S, Godwin AK, Bell DW, Liu Z, Hogan M, Yakushiji M, Testa JR.

Department of Medical Oncology, Fox Chase Cancer Center Philadelphia, Pennsylvania, USA.

Comparative genomic hybridization (CGH) was used in a retrospective analysis of chromosomal imbalances in frozen primary tumor specimens from 14 endometrial carcinoma patients. Chromosome changes were detected in nine cases (64%), and tumor stage and grade tended to parallel the degree of genomic imbalances. Gain of the entire long arm of chromosome 1 was observed in six cases (43%), three of which displayed only this chromosome change. Other common sites of copy number increases included 8q21-->qter (4 cases), 10p15 (4 cases), 10q11-->q24 (3 cases), and 13q21-->qter (3 cases, each with stage III disease). Two of the tumors with gains of chromosome 10 involved the whole chromosome, and this was the sole abnormality in one case. DNA amplification at 5p14-->p15 was identified in one specimen, a stage III tumor having numerous imbalances. DNA microsatellite analysis revealed multiple replication errors (RER), indicative of the RER+ phenotype, in four of 13 (31%) cases evaluated. The RER+ phenotype was observed in four of six stage Ia tumors but in none of seven stage Ib or stage III tumors. Multiple genomic imbalances detected by CGH were not observed in RER+ tumors but were detected in five of nine tumors without the RER+ phenotype. These investigations demonstrate the feasibility of CGH for the retrospective assessment of chromosomal changes in endometrial carcinoma specimens. Moreover, these data suggest that the etiologies in tumors with and without the RER+ phenotype may differ.

PMID: 9115961 [PubMed - indexed for MEDLINE]

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1: Acta Biochim Pol 2001;48(4):921-33

Protein phosphatase 2A: variety of forms and diversity of functions.

Lechward K, Awotunde OS, Swiatek W, Muszynska G.

Cell and Molecular Signaling Laboratory, Intercollegiate Faculty of Biotechnology Medical University of Gdansk, Poland.

Protein phosphatase 2A (PP2A) comprises a diverse family of phosphoserine- and phosphothreonine-specific phosphatases present in all eukaryotic cells. All forms of PP2A contain a catalytic subunit (PP2Ac) which forms a stable complex with the structural subunit PR65/A. The heterodimer PP2Ac-PR65/A associates with regulatory proteins, termed variable subunits, in order to form trimeric holoenzymes attributed with distinct substrate specificity and targeted to different subcellular compartments. PP2Ac activity can be modulated by reversible phosphorylation on Tyr307 and methylation on C-terminal Leu309. Studies on PP2A have shown that this enzyme may be implicated in the regulation of metabolism, transcription, RNA splicing, translation, differentiation, cell cycle, oncogenic transformation and signal transduction.

Publication Types:
- Review
- Review, Tutorial

PMID: 11996003 [PubMed - indexed for MEDLINE]

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1: J Med Chem 2002 Mar 14;45(6):1151-75 Related Articles, Books, LinkOu

Serine-threonine protein phosphatase inhibitors: development of potential therapeutic strategies.

McCluskey A, Sim AT, Sakoff JA.

School of Biological & Chemical Science, Medicinal Chemistry Group, The University of Newcastle, Callaghan, NSW 2308, Australia. amcclusk@mail.newcastle.edu.au

Publication Types:
- Review
- Review, Tutorial

PMID: 11881984 [PubMed - indexed for MEDLINE]

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1: J Cell Sci 2002 Jan 15;115(Pt 2):241-56

Protein phosphatase 1--targeted in many directions.

Cohen PT.

Medical Research Council Protein Phosphorylation Unit, School of Life Sciences, University of Dundee, Dundee DD15EH, Scotland, UK. p.t.w.cohen@dundee.ac.uk

Protein phosphatase 1 (PP1) is a major eukaryotic protein serine/threonine phosphatase that regulates an enormous variety of cellular functions through the interaction of its catalytic subunit (PP1c) with over fifty different established or putative regulatory subunits. Most of these target PP1c to specific subcellular locations and interact with a small hydrophobic groove on the surface of PP1c through a short conserved binding motif--the RVxF motif--which is often preceded by further basic residues. Weaker interactions may subsequently enhance binding and modulate PP1 activity/specificity in a variety of ways. Several putative targeting subunits do not possess an RVxF motif but nevertheless interact with the same region of PP1c. In addition, several 'modulator' proteins bind to PP1c but do not possess a domain targeting them to a specific location. Most are potent inhibitors of PP1c and possess at least two sites for interaction with PP1c, one of which is identical or similar to the RVxF motif.Regulation of PP1c in response to extracellular and intracellular signals occurs mostly through changes in the levels, conformation or phosphorylation status of targeting subunits. Understanding of the mode of action of PP1c complexes may facilitate development of drugs that target particular PP1c complexes and thereby modulate the phosphorylation state of a very limited subset of proteins.

Publication Types:
- Review
- Review, Academic

PMID: 11839776 [PubMed - indexed for MEDLINE]

1: Mol Psychiatry 2002;7(6):542-59

Genome-wide scans of three independent sets of 90 Irish multiplex schizophrenia families and follow-up of selected regions in all families provides evidence for multiple susceptibility genes.

Straub RE, MacLean CJ, Ma Y, Webb BT, Myakishev MV, Harris-Kerr C, Wormley B, Sadek H, Kadambi B, O'Neill FA, Walsh D, Kendler KS.

Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA, and Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA.

From our linkage study of Irish families with a high density of schizophrenia, we have previously reported evidence for susceptibility genes in regions 5q21-31, 6p24-21, 8p22-21, and 10p15-p11. In this report, we describe the cumulative results from independent genome scans of three a priori random subsets of 90 families each, and from multipoint analysis of all 270 families in ten regions. Of these ten regions, three (13q32, 18p11-q11, and 18q22-23) did not generate scores above the empirical baseline pairwise scan results, and one (6q13-26) generated a weak signal. Six other regions produced more positive pairwise and multipoint results. They showed the following maximum multipoint H-LOD (heterogeneity LOD) and NPL scores: 2p14-13: 0.89 (P = 0.06) and 2.08 (P = 0.02), 4q24-32: 1.84 (P = 0.007) and 1.67 (P = 0.03), 5q21-31: 2.88 (P= 0.0007), and 2.65 (P = 0.002), 6p25-24: 2.13 (P = 0.005) and 3.59 (P = 0.0005), 6p23: 2.42 (P = 0.001) and 3.07 (P = 0.001), 8p22-21: 1.57 (P = 0.01) and 2.56 (P = 0.005), 10p15-11: 2.04 (P = 0.005) and 1.78 (P = 0.03). The degree of 'internal replication' across subsets differed, with 5q, 6p, and 8p being most consistent and 2p and 10p being least consistent. On 6p, the data suggested the presence of two susceptibility genes, in 6p25-24 and 6p23-22. Very few families were positive on more than one region, and little correlation between regions was evident, suggesting substantial locus heterogeneity. The levels of statistical significance were modest, as expected from loci contributing to complex traits. However, our internal replications, when considered along with the positive results obtained in multiple other samples, suggests that most of these six regions are likely to contain genes that influence liability to schizophrenia.

PMID: 12140777 [PubMed - in process]

1: Genes Immun 2002 Aug;3(5):279-85

A genome-wide screen for linkage in Nordic sib-pairs with multiple sclerosis.

Akesson E, Oturai A, Berg J, Fredrikson S, Andersen O, Harbo HF, Laaksonen M, Myhr KM, Nyland HI, Ryder LP, Sandberg-Wollheim M, Sorensen PS, Spurkland A, Svejgaard A, Holmans P, Compston A, Hillert J, Sawcer S.

University of Cambridge, Neurology unit, Addenbrooke's Hospital, Cambridge, UK, and Department of Neurology, Karolinska Institutet at Huddinge University Hospital, Stockholm, Sweden.

Genetic factors influence susceptibility to multiple sclerosis but the responsible genes remain largely undefined, association with MHC class II alleles being the only established genetic feature of the disease. The Nordic countries have a high prevalence of multiple sclerosis, and to further explore the genetic background of the disease, we have carried out a genome-wide screen for linkage in 136 sibling-pairs with multiple sclerosis from Denmark, Finland, Norway and Sweden by typing 399 microsatellite markers. Seventeen regions where the lod score exceeds the nominal 5% significance threshold (0.7) were identified-1q11-24, 2q24-32, 3p26.3, 3q21.1, 4q12, 6p25.3, 6p21-22, 6q21, 9q34.3, 10p15, 10p12-13, 11p15.5, 12q21.3, 16p13.3, 17q25.3, 22q12-13 and Xp22.3. Although none of these regions reaches the level of genome-wide significance, the number observed exceeds the 10 that would be expected by chance alone. Our results significantly add to the growing body of linkage data relating to multiple sclerosis.

PMID: 12140746 [PubMed - in process]

1: Am J Psychiatry 2002 May;159(5):803-12

A genome-wide scan for linkage to chromosomal regions in 382 sibling pairs with schizophrenia or schizoaffective disorder.

DeLisi LE, Shaw SH, Crow TJ, Shields G, Smith AB, Larach VW, Wellman N, Loftus J, Nanthakumar B, Razi K, Stewart J, Comazzi M, Vita A, Heffner T, Sherrington R.

Department of Psychiatry, New York University, New York, NY 10016, USA. DeLisi76@aol.com

OBJECTIVE: Some genome-wide scans and association studies for schizophrenia susceptibility genes have yielded significant positive findings, but there is disagreement between studies on their locations, and no mutation has yet been found in any gene. Since schizophrenia is a complex disorder, a study with sufficient power to detect a locus with a small or moderate gene effect is necessary. METHOD: In a genome-wide scan of 382 sibling pairs with a diagnosis of schizophrenia or schizoaffective disorder, 396 highly polymorphic markers spaced approximately 10 centimorgans apart throughout the genome were genotyped in all individuals. Multipoint nonparametric linkage analysis was performed to evaluate regions of the genome demonstrating increased allele sharing, as measured by a lod score. RESULTS: Two regions with multipoint maximum lod scores suggesting linkage were found. The highest lod scores occurred on chromosome 10p15-p13 (peak lod score of 3.60 at marker D10S189) and the centromeric region of chromosome 2 (peak lod score of 2.99 at marker D2S139). In addition, a maximum lod score of 2.00 was observed with marker D22S283 on chromosome 22q12, which showed evidence of an imprinting effect, whereby an excess sharing of maternal, but not paternal, alleles was present. No evidence of linkage was obtained at several locations identified in previous studies, including chromosomes 1q, 4p, 5p-q, 6p, 8p, 13q, 15p, and 18p. CONCLUSIONS: The findings of this large genome-wide scan emphasize the weakness and fragility of linkage reports on schizophrenia. No linkage appears to be consistently replicable across large studies. Thus, it has to be questioned whether the genetic contribution to this disorder is detectable by these strategies and the possibility raised that it may be epigenetic, i.e., related to gene expression rather than sequence variation. Nevertheless, the positive findings on chromosome 2, 10, and 22 should be pursued further.

Publication Types:
- Multicenter Study

1: Br J Cancer 2001 Nov 16;85(10):1510-4

Related Articles, Books, LinkOut

BJC British Journal of Cancer

hTR repressor-related gene on human chromosome 10p15.1.

Miura N, Onuki N, Rathi A, Virmani A, Nakamoto S, Kishimoto Y, Murawaki Y, Kawasaki H, Hasegawa J, Oshimura M, Travis WD, Gazdar AF.

Hamon Center for Therapeutic Oncology Research, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas 75390-8593, USA.

Somatic cells express genes that suppress telomerase activity and these genes may be inactivated in tumour cells. We postulated that cancer cells acquire immortality by activation of telomerase by the loss of such a gene. We have reported recently that a telomerase repressor gene may be located on 10p15.1 by deletion mapping using microcell-mediated chromosome transfer (MMCT), radiated microcell fusion (RMF), fluorescent in situ hybridization (FISH) and STS analysis. To independently confirm this result, we correlated expression of RNA component of telomerase (hTR) as a marker of telomerase expression by in situ hybridization with allelic loss in pulmonary carcinoid tumours. Unlike most malignant tumours, pulmonary carcinoids (which are low-grade malignant tumours) are heterogeneous for telomerase expression. Loss of 5 closely spaced polymorphic markers on 10p15.1, especially D10S1728, were highly correlated with hTR expression. In an additional experiment, 10p15.1 showed higher and more significant correlation than any region of 3p where it has been predicted as another chromosomal location of telomerase repressor with allelic loss of the region. Our findings strongly suggest that 10p15.1 harbours a gene involved in repression of telomerase RNA component in human somatic cells and each putative repressor (on 3p and 10p) may act independently.

PMID: 11720437 [PubMed - indexed for MEDLINE]

1: Oncogene 2001 Feb 15;20(7):828-35

Functional evidence for a telomerase repressor gene on human chromosome 10p15.1.

Nishimoto A, Miura N, Horikawa I, Kugoh H, Murakami Y, Hirohashi S, Kawasaki H, Gazdar AF, Shay JW, Barrett JC, Oshimura M.

Department of Molecular and Cell Genetics, School of Life Sciences, Faculty of Medicine, Tottori University, Yonago, Tottori 683-8503, Japan.

Based on the sites of frequent allelic loss in hepatocellular carcinoma, five normal human chromosomes (2, 4, 5, 10 and 16) were transferred individually into a telomerase-positive human hepatocellular carcinoma cell line, Li7HM, by microcell-mediated chromosome transfer (MMCT). Chromosome 10, but not the others, repressed telomerase activity immediately and stopped cell growth after 50 population doublings (PDs). Loss of the transferred 10p loci resulted in the emergence of revertant cells that continued to proliferate and expressed telomerase activity, suggesting the presence of a telomerase repressor gene on this chromosomal arm. Transfer of a series of defined fragments from chromosome 10p successfully narrowed down the responsible region: a 28.9-cM region on 10p15 (between WI-4752 and D10S249), but not a 26.2-cM region (between D10S1728 and D10S249), caused repression of telomerase activity and progressive telomere shortening. A strong correlation between the expression level of telomerase catalytic subunit gene (hTERT) and telomerase activity was observed. These findings suggest that a novel telomerase repressor gene which controls the expression of hTERT is located on the 2.7-cM region (between WI-4752 and D10S1728) on chromosome 10p15.1.

PMID: 11314017 [PubMed - indexed for MEDLINE]

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1: Oncogene 2001 Jan 18;20(3):314-9 Related Articles, Books, LinkOut

Functional evidence for the presence of tumor suppressor gene on chromosome 10p15 in human prostate cancers.

Fukuhara H, Maruyama T, Nomura S, Oshimura M, Kitamura T, Sekiya T, Murakami Y.

Tumor Suppression & Functional Genomics Project, National Cancer Center Research Institute, Tokyo 104-0045, Japan.

Loss of heterozygosity on chromosome 10p was observed frequently in human prostate cancers. Studies have demonstrated that the introduction of the short arm of human chromosome 10 into a human prostate cancer cell line, PPC-1, by microcell-mediated chromosome transfer (MMCT), suppressed the malignant phenotype, suggesting the presence of a prostate tumor suppressor gene(s) within a region of 17 cM at distal 10p. To narrow down the candidate region harboring the tumor suppressor gene, a series of 10p fragments were transferred into PPC-1 cells by MMCT using a panel of hamster-human hybrid cells containing various portions of 10p. Four of the six hybrid cells obtained showed decreased tumorigenicity when injected subcutaneously into athymic nude mice. Tumors developed only at six of 40 injection sites for these four hybrid cells. In contrast, the other two hybrid cells, as well as parental PPC-1 cells, were judged to be fully tumorigenic because tumors appeared at a total 26 of 32 sites for the two hybrid cells and 15 of 16 sites for PPC-1. Allelotyping of 10p combined with fluorescence in situ hybridization in these hybrid cells suggested that a prostate tumor suppressor gene was located within a fragment of approximately 1.2 Mb flanked by D10S1172 and D10S226 on 10p15.1.

PMID: 11313960 [PubMed - indexed for MEDLINE]

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1: Genomics 2000 Aug 1;67(3):268-72

A sequence-ready BAC clone contig of human chromosome 10p15 spanning the loss of heterozygosity region in glioma.

Harada K, Nishizaki T, Maekawa K, Kubota H, Harada K, Suzuki M, Ohno T, Sasaki K, Soeda E.

Department of Pathology, Department of Neurosurgery, Yamaguchi University School of Medicine, Japan. kharada@po.cc.yamaguchi-u.ac.jp

Deletion of chromosome 10 is one of the most common chromosomal alterations in glioma. At 10p15, the telomeric region of the short arm of chromosome 10, loss of heterozygosity (LOH) has been frequently observed by microsatellite analysis, suggesting the presence of a tumor suppressor gene. We examined LOH in 34 gliomas on chromosome 10, and frequent LOH on 10p was detected on 10p15, in agreement with deletion mapping studies on chromosome 10. We then constructed a bacterial artificial chromosome (BAC) clone contig covering the critical region, which spanned the interval between D10S249 and D10S533 on 10p15. The map contained 68 BAC clones connected by 74 sequenced tag sites (STSs) and covered approximately 2.7 Mb, with one gap. A total of 74 STSs, including 6 microsatellite markers, 29 expressed sequenced tags (ESTs), and 39 BAC end STSs, were physically arranged. Twenty-eight ESTs were mapped in the interval between D10S249 and D10S559 (approximately 1200 kb), and another EST was mapped in the interval between D10S559 and D10S533 (approximately 1300 kb). This sequence-ready BAC clone contig map will be a basic resource for high-quality sequencing and positional cloning of the putative tumor suppressor gene at 10p15 in glioma. Copyright 2000 Academic Press.

PMID: 10936048 [PubMed - indexed for MEDLINE]

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1: Cancer Res 1999 Aug 1;59(15):3596-601

The chromosome 10 monosomy common in human melanomas results from loss of two separate tumor suppressor loci.

Robertson GP, Herbst RA, Nagane M, Huang HJ, Cavenee WK.

Ludwig Institute for Cancer Research, University of California at San Diego, La Jolla 92093-0660, USA. gprobertson@ucsd.edu

Alteration of chromosome 10 is common in human melanomas and usually entails the loss of an entire chromosome homologue. Although the reasons for monosomy in cancer has remained obscure, one possibility is that multiple tumor suppressor genes residing on this chromosome must be lost in unison during tumor progression, and this is easier to accomplish by chromosome segregation rather than by multiple mutational and/or deletion events. The localization and identification of these genes has been hampered by the monosomy itself, which has resulted in a paucity of small defining deletions in tumors. Here, we have addressed the issue of monosomy in tumor development by using functional complementation mapping to localize and demonstrate the existence of different melanoma suppressor genes on chromosome 10 and assigned each locus a distinct tumorigenic phenotype. We report that a locus on 10q distal to 10q23.1, likely involving the PTEN tumor suppressor, causes a severe reduction in the kinetics of melanoma tumor formation in animals. In contrast, a previously unrecognized region at 10p15.3 has a distinct, but lesser, effect on in vivo melanoma growth. Thus, the loss of both of these regions, which is accomplished by tumor-associated monosomy, provides a significant growth advantage over the individual loss of either region, thereby explaining the monosomy observed in sporadic melanomas.

PMID: 10446968 [PubMed - indexed for MEDLINE]

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1: Cytogenet Cell Genet 1998;83(3-4):214-7 Related Articles, Nucleotide, OMIM, Protein, Books, LinkOut

KARGER Full Text

Molecular cloning, expression, and chromosomal localization of a ubiquitously expressed human 6-phosphofructo-2-kinase/ fructose-2, 6-bisphosphatase gene (PFKFB3).

Manzano A, Rosa JL, Ventura F, Perez JX, Nadal M, Estivill X, Ambrosio S, Gil J, Bartrons R.

Unitat de Bioquimica, Campus de Bellvitge, Universitat de Barcelona, Barcelona, Spain.

We report the identification of a human 6-phosphofructo-2-kinase/fructose 2,6-bisphosphatase gene (PFKFB3) isolated from a human fetal brain cDNA library. The gene was localized to 10p15-->p14 by fluorescence in situ hybridization. The entire cDNA (4,322 bp) codes for a polypeptide of 520 amino acid residues (molecular weight, 59.571 kDa). Structural analysis showed the presence of a kinase domain located at the amino terminus and a bisphosphatase domain at the carboxy terminus, characteristic of previously described 6-phosphofructo-2-kinase/fructose 2, 6-bisphosphatase isozymes. In addition, a phosphorylation site for cAMP-dependent protein kinase was found at the carboxy terminus. Northern blot analysis showed the presence of a unique 4.8-kb mRNA expressed in the different tissues studied. In mammalian COS-1 cells, this cDNA drives the expression of an active isozyme. Taken together, these results identify the presence of a gene coding for a human 6-phosphofructo-2-kinase/fructose 2,6-bisphosphatase isozyme which is ubiquitously expressed.

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1: Clin Genet 1999 Apr;55(4):269-76

online

Partial DiGeorge syndrome in two patients with a 10p rearrangement.

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We describe 2 patients with a partial DiGeorge syndrome (facial dysmorphism, hypoparathyroidism, renal agenesis, mental retardation) and a rearrangement of chromosome 10p. The first patient carries a complex chromosomal rearrangement, with a reciprocal insertional translocation between the short arm of chromosome 10 and the long arm of chromosome 8, with karyotype 46, XY ins(8;10) (8pter 8q13::10p15-->10p14::8q24.1-->8qter) ins(10:8) (10pter--> 10p15::8q24.1-->8q13::10p14-->10qter). The karyotype of the second patient shows a terminal deletion of the short arm of chromosome 10. In both patients, the breakpoints on chromosome 10p reside outside the previously determined DiGeorge critical region II (DGCRII). This is in agreement with previous reports of patients with a terminal deletion of 10p with breakpoints distal to the DGCRII and renal malformations/hypoparathyroidism, and thus adds to evidence that these features may be caused by haploinsufficiency of one or more genes distal to the DGCRII.

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1: Annu Rev Pharmacol Toxicol 2002;42:209-34

Protein tyrosine phosphatases: structure and function, substrate specificity, and inhibitor development.

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Protein tyrosine phosphatases (PTPs) are signaling enzymes that control a diverse array of cellular processes. Malfunction of PTP activity is associated with a number of human disorders. Recent genetic and biochemical studies indicate that PTPs represent a novel platform for drug discovery. Detailed knowledge of PTP substrate specificity and the wealth of structural data on PTPs provide a solid foundation for rational PTP inhibitor design. This review summarizes a correlation of PTP structure and function from mutagenesis experiments. The molecular basis for PTP1B and MKP3 substrate recognition is discussed. A powerful strategy is presented for creating specific and high-affinity bidentate PTP inhibitors that simultaneously bind both the active site and a unique adjacent site. Finally, recent advances in the development of potent and selective inhibitors for PTP1B and Cdc25 are described.

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